II. REMARKS

Formal Matters

Claims 31, 35-38, 40-47, 51, 52, 56, 59, 60, and 62-65 are pending after entry of the above-noted amendments.

Claims 31, 35-38, 41-47, 51, 52, 56, 57, and 59-61 were examined and were rejected. Claim 40 was withdrawn from consideration.

Claims 31, 40, 41, and 56 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. Support for "wherein the ErbB1 inhibitor interacts with an ErbB1 receptor" is found in the specification at, e.g., paragraph 0040. No new matter is added by the claim amendments.

Claims 57 and 61 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Claims 62-65 are added. No new matter is added by new claims 62-65. Support for the new claims is found in the claims as originally filed, and throughout the specification.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Claim objections

Claims 57 and 60 were objected to.

Claim 57

The Office Action stated that in the phrase "expression of LAMC2 or GPC3 genes or gene, wherein" the recitation "genes or gene" appears to be an editing error.

Claim 57 is cancelled without prejudice to renewal, thereby rendering this objection moot.

Claim 60

The Office Action stated that claim 60 recites transcripts that have not been elected.

Applicants are not required to cancel non-elected species from claims. Indeed, upon allowance of a generic claim, Applicants are entitled to consideration of non-elected species.

Rejection under 35 U.S.C. §112, first paragraph

Claims 31, 35-38, 41-47, 51, 52, 56, 57, and 59-61 were rejected under 35 U.S.C. §112, first paragraph, as allegedly reciting new matter. Claims 31, 35-38, 41-47, 51, 52, 56, 57, and 59-61 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement.

"New matter"

The Office Action stated that the specification does not appear to provide support for the amendment to claim 31 which recites "ErbB1 inhibitor." The Office Action stated that the specification discloses the genus of EGF receptors, and stated that the specification does not disclose a single species within this genus. Applicants respectfully traverse the rejection.

"ErbB1" is synonymous with "EGFR." As such, claim 31 does not recite new matter.

As described in the instant application, the epidermal growth factor receptor (EGFR) family includes: 1) EGFR; 2) erb-B2; 3) erb-B3; and 4) erb-B4. Specification, paragraph 0079. The amendment to "ErbB1" was made merely to clarify that, of the family of EGF receptors, the receptor being referred to is the EGFR (also known as ErbB1). See, e.g., Oda et al. ((2005) *Molec. Systems Biol.* 1:2005.0010), which states:

> The binding of ligands induces homo- and heterodimerization of four ErbB family receptors: EGFR (ErbB1), ErbB2, ErbB3, and ErbB4 (Yarden and Schlessinger, 1987; Yarden and Sliwkowski, 2001). Although 10 combinations of ErbB receptor

Oda, page 3, column 2, second full paragraph.

Similarly, Moulder et al. ((2001) *Cancer Res.* 61:8887) states:

> The EGFR[3] (HER1, erbB1), HER2/neu (erbB2), HER3 (erbB3), and HER4 (erbB4) are members of the erbB family of transmembrane tyrosine kinases. Except for HER2, binding of receptor-specific li-

Moulder, page 61, column 1, first paragraph under "Introduction."

Thus, even before the November 15, 2002 priority date of the instant application, "EGFR" and "ErbB1" were known to be synonyms.

Applicants also provide herewith a copy of two entries from the National Cancer Institute's on-line Dictionary of Cancer Terms, which entries show that EGFR and ErbB1 are synonyms.

Enablement

The Office Action stated that "the specification has not taught a reliable method of associating increased levels of LAMC2 and GPC3 and the response to ErbB1 inhibitors." Office Action, page 14. The Office Action stated that "although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the claimed invention." Office Action, page 14. Applicants respectfully traverse the rejection.

Comments regarding the claimed invention

Applicants have provided clinical data that were shown to be statistically significant. Normalized expression levels of various genes were examined; several of the normalized levels of these various genes correlated with patient response to treatment with an ErbB1 inhibitor.

As set out in the instant specification at paragraph 0028, "normalized" with respect to a gene transcript or a gene expression produce refers to the level of the transcript or the gene expression product relative to the mean levels of transcripts/products of a set of reference genes. The set of reference genes are either selected based on their minimal variation across patients, tissues, or treatments (e.g., "housekeeping genes"), or the reference genes are the totality of tested genes. This normalization reduces variation in the absolute amount of a particular transcript, so that a correlation can be drawn between patient response and normalized expression level.

The inventors have found that a normalized expression level of LAMC2 and the likelihood that a patient having an ErbB1-expressing colon cancer will respond to an ErbB1 inhibitor are correlated. The higher the normalized level of a LAMC2 transcript, the less likely it is that the patient will respond to treatment with an ErbB1 inhibitor, and vice versa.

The instant claims are supported by an enabling disclosure.

To comply with 35 U.S.C. § 112, first paragraph, a specification need only enable a skilled artisan to make and use the claimed invention without undue experimentation. Accordingly, a specification complies with the statute even if a reasonable amount of experimentation is required, as long as the experimentation is not "undue." One way to determine if undue experimentation is required is to analyze the subject specification in light of the *Wands* factors:[1] (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. However, all of the factors need not be reviewed when determining whether a disclosure is enabling.[2]

Applicants respectfully submit that when evaluated in view of the relevant *Wands* factors, the specification clearly enables one of skill in the art to practice the subject invention without undue experimentation. In other words, claims 31, 35-38, 41-47, 51, 52, 56, 57, and 59-61 recite subject matter that is adequately described in the specification in such a way as to teach a skilled artisan how to make and use the

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[1] *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988)
[2] See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991).

claimed invention without having to practice undue experimentation. An analysis of the *Wands* factors is provided below.

- **the breadth of the claims**

The claims currently under examination involve predicting the likelihood that a human colon cancer patient will respond to treatment with an ErbB1 inhibitor based on the expression level of a gene such as LAMC2. While the term "ErbB1 inhibitor" encompasses various agents, as noted in the specification, Applicants have presented data (e.g., Declaration of Joffre Baker; provided to the Office on December 21, 2006) showing that, in a study of patients treated with an EGFR inhibitor selected from erlotinib, gefitinib, Cetuximab (which was inadvertently referred to in the Baker Declaration as "cytoximab"), EMD72000 (which was inadvertently referred to in the Baker Declaration as EMB72000), and AEE788, a correlation between response to treatment with EGFR inhibitor and LAMC2 levels was made. Dr. Baker stated that the data indicate that overexpression of LAMC2 in colon tumor tissue showed a negative (e.g., inverse) correlation with response to treatment with any of the EGFR inhibitors. The data were provided in Example 2 of the instant application.

Erlotinib (*N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy) quinazolin-4-amine; also known by its trade name Tarceva®) is a quinazoline compound that is an EGFR tyrosine kinase inhibitor. Specification, paragraph 0082.

Gefitinib (*N*-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-amine; also known as ZD1839 or Iressa) is another quinazoline compound that is an EGFR tyrosine kinase inhibitor. Specification, paragraph 0079.

Cetuximab (marketed under the name Erbitux) is a chimeric monoclonal antibody that is an EGFR inhibitor. Specification, paragraph 0081.

EMD72000 (also known as matuzumab) is a humanized anti-EGFR monoclonal antibody.

AEE788 is a 7H-pyrrolo[2,3-d] pyrimidine that is an EGFR inhibitor.

Thus, Applicants have shown a negative correlation between LAMC2 transcript levels and patient response to at least **three** classes of EGFR inhibitor, namely to:

1) EGFR inhibitors of the quinazoline class;

2) EGFR inhibitors of the monoclonal antibody class; and

3) EGFR inhibitors of the pyrrolopyrimidine class.

A number of ErbB1 inhibitor compounds of these and other classes were known in the art as of the November 15, 2002 priority date of the instant application; and the instant application lists several known ErbB1 inhibitors. Furthermore, it should be noted that ligand-bound ErbB1 acts by activating certain well-known signaling pathways. It has been shown amply in the literature that these signaling pathways can be disrupted by

any of a wide variety of ErbB1 inhibitors of a number of different classes.

- **the nature of the invention**

The Office Action stated that the "nature of the invention requires the knowledge of a reliable association between the levels of LAMC2 or GCP3 in a sample and how a patient will respond to treatment with an ErbB1 inhibitor." Office Action, bridging sentence, pages 6 and 7.

Applicants have provided ample guidance in the specification that indicates that there is an inverse correlation between response of a patient to treatment with an EGFR (ErbB1) inhibitor and LAMC2 transcript levels. The data indicate that overexpression of LAMC2 in colon tumor tissue showed a negative correlation with response to treatment with any of the ErbB1 inhibitors. The data were provided in Example 2 of the instant application.

As noted above, as attested to by Dr. Joffre Baker, the data show a negative (inverse) correlation between LAMC2 transcript levels and patient response to at least three classes of ErbB1 inhibitor, namely to: 1) ErbB1 inhibitors of the quinazoline class; 2) ErbB1 inhibitors of the monoclonal antibody class; and 3) ErbB1 inhibitors of the pyrrolopyrimidine class.

- **scope of the claims**

The Office Action stated that the scope of the claims is broad over the recitation of: "a higher normalized level," "decreased likelihood," "response," and "ErbB1 inhibitor."

As noted above, Applicants have presented data showing an inverse correlation between patient response to a number of ErbB1 inhibitors of various classes and normalized LAMC2 transcript levels. As such, those skilled in the art would find it reasonable to expect that an inverse correlation between patient response to other ErbB1 inhibitors and normalized LAMC2 levels would also be observed.

The specification describes how the levels of gene expression were measured, normalized, and evaluated. Specification, paragraph 0095. The specification indicates that certain genes were identified as "statistically significant." Those skilled in the art would understand that a "higher" level would refer to a statistically significant higher level. Similarly, those skilled in the art would understand that a "decreased likelihood" would refer to a statistically significant decreased likelihood.

Nevertheless, and solely in the interest of expediting prosecution, claim 31 is amended to delete recitation of "higher normalized level" and "decreased likelihood."

The Office Action stated that the term "response" is broad because it encompasses "any type of response (remission of cancer, side effects, etc.)." Office Action, page 7.

However, those in the field would understand that "response" to an ErbB1 inhibitor would refer to a response in terms of the cancer itself, e.g., decreased tumor load, reduction in cancer cell number, and the like.

- **the amount of direction or guidance presented**

The Office Action stated that the specification never discusses ErbB1 or ErbB1 inhibitors in particular.

However, as noted above, ErbB1 is another name for "EGFR." The instant specification discloses a number of EGFR inhibitors. For example, the specification states:

> Several EGFR inhibitors, such as **ZD1839** (also known as gefitinib or Iressa); and OSI774 (**Erlotinib**, Tarceva™), are promising drug candidates for the treatment of EGFR-expressing cancer.
> Iressa, a small synthetic quinazoline, competitively inhibits the ATP binding site of EGFR, a growth-promoting receptor tyrosine kinase, and has been in Phase III clinical trials for the treatment of non-small-cell lung carcinoma. Another EGFR inhibitor, [agr]cyano-[bgr]methyl-*N*-[(trifluoromethoxy)phenyl]-propenamide (**LFM-A12**), has been shown to inhibit the proliferation and invasiveness of EGFR positive human breast cancer cells.
> **Cetuximab** is a monoclonal antibody that blocks the EGFR and EGFR-dependent cell growth. It is currently being tested in phase III clinical trials.

Instant specification, paragraphs 0079-0081, emphasis added.

Furthermore, a number of additional ErbB1 inhibitors were known in the art as of the November 15, 2002 priority date.

The Office Action discussed the data presented in the working examples, and stated that "the specification does not teach which EGFR inhibitors were used in the study." Office Action, page 9.

However, as discussed above, the Declaration of Joffre Baker indicates that various classes of EGFR inhibitors were used, and with **each class** of EGFR inhibitor, there was an inverse correlation between the level of LAMC2 transcript and patient response. In fact, a number of the inhibitors that were used were the same as those listed in the instant application.

- **the presence or absence of working examples**

Compliance with the enablement requirement under 35 U.S.C. §112, first paragraph, does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the

invention without undue experimentation.[3] Furthermore, "Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."[4]

Nevertheless, as discussed above, working examples were in fact provided, which demonstrated a correlation between LAMC2 transcript levels and patient response to EGFR inhibitor treatment.

The specification in Example 2 describes a method of extracting RNA from paraffin-embedded, formalin fixed tumor tissue from 23 patients diagnosed with colon cancer. The samples were taken from the patients prior to treatment with the EGFR inhibitor. The Example describes the procedure for quantitative gene expression using RT-PCR on the RNA samples. In the example, tumor tissue was analyzed for 192 genes. The results were analyzed based on complete or partial response as one group and stable disease or progressive disease as the other group. Table 3 shows that overexpression of LAMC2 correlated with resistance to EGFR inhibitors.

- **the relative skill of those in the art**

The Office Action acknowledged that the level of skill in the art is high.

- **the predictability or unpredictability of the art**

In making this rejection, the Examiner asserted that the state of the art at the time of Applicants' filing was "underdeveloped" with regard to the use of RNA transcripts, such as LAMC2 transcripts, to predict the likelihood that a patient with an ErbB1 colon cancer will respond to treatment with an ErbB1 inhibitor.

First, the courts have clearly taught that even in unpredictable arts the specification does not have to disclose every species of a genus that would work and every species that would not work.

As has been very clearly explained[5]:

> "To require such a complete disclosure would apparently necessitate a patent application or applications with thousands of catalysts....More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used ...."

The claims of the instant application relate to predicting a patient's response to an ErbB1 inhibitor based

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[3] In re Borkowski, 164 USPQ 642,645 (CCPA 1970).
[4] *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).
[5] *In re Angstadt*, 190 USPQ 214, at 219 (CCPA 1976)

on the level of a LAMC2 transcript. As noted above, Applicants showed an inverse correlation between LAMC2 transcript level and patient response to **at least three classes** of EGFR inhibitor. Thus, those skilled in the art would reasonably expect that patient response to EGFR inhibitors other than those specifically exemplified would exhibit an inverse correlation with LAMC2 transcript levels. Since one of skill in the art would recognize that a reasonable correlation exists between patient response to EGFR inhibitors of the genus "ErbB1 inhibitor" and LAMC2 transcript level, and since every species in a genus does not have to be tested for a genus to be enabled, extensive disclosure or guidance of the active species of a genus does not have to be provided for a genus of this scope to be enabled.

Secondly, the publications cited in the Office Action do not support a conclusion that the instant claims are not supported by an enabling disclosure.

The Office Action cited certain publications to support the assertion that the state of the art at the time of Applicants' filing was "underdeveloped" with regard to the use of RNA transcripts, such as LAMC2 transcripts, to predict the likelihood that a patient with an ErbB1 colon cancer will respond to treatment with an ErbB1 inhibitor.

Evans

The Office Action cited Evans ((2004) *Nature* 429:464; "Evans"), and stated that Evans teaches that most drug effects and treatment outcomes are determined by an interplay of multiple genes, and that Evans teaches that although single gene defects can have a strong effect on their substrates, most of the phenotypic variability in drug response remains unexplained despite numerous efforts to interrogate candidate genes and pathways.

First, it is noted that the statement that "most of the phenotypic variability in drug response remains unexplained despite numerous efforts to interrogate candidate genes and pathways" relates to a discussion of patient response to anti-hypertensive drugs, not to patient response to EGFR inhibitors. Thus, the cited statement, when taken in context, does not support a conclusion that the instant claims lack enablement.

Secondly, as noted above, Applicants demonstrated a statistically significant correlation between LAMC2 transcript levels and patient response to EGFR inhibitors belonging to at least three different classes of EGFR inhibitor. Thus, Applicants' data support the fact that the instant claims are enabled.

Lee

The Office Action cited Lee et al. ((2005) *The Oncologist* 10:104; "Lee"), and stated that Lee teaches that while genes likely contribute to the observed variability in cancer treatment outcome, there are several other variables that have been found to be associated with drug responses such as age, gender, diet, and drug-drug interactions.

The gist of the Lee reference is captured in the title: "Cancer pharmacogenomics: powerful tools in cancer

chemotherapy and drug development." Lee focuses on the promise of correlations between genetics and an individual's response to treatment with a therapeutic agent. If anything, Lee would tend to support a conclusion that the instant claims comply with the enablement requirement of 35 U.S.C. §112, first paragraph.

Wu

The Office Action cited Wu et al. ((2001) *J. Pathol.* 195:53; "Wu"), and stated that Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge.

It is unclear how the cited passages of Wu might support the assertion that instant claims 31, 35-38, 41-47, 51, 52, 56, 57, and 59-61 lack enablement. Applicants respectfully request clarification.

Newton

The Office Action cited Newton et al. ((2001) *J. Computational Biol.* 8:37; "Newton"), and stated that Newton teaches the difficulty in applying gene expression results. The Office Action stated that Newton teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation.

The Office Action stated that there is no replication of data in the instant specification.

As noted above, Applicants provided clinical data that was shown to be statistically significant. Applicants provided data that show a correlation between normalized LAMC2 transcript levels and patient response to a variety of ErbB1 inhibitors. As such, Newton is irrelevant to enablement of the instant claims.

Lucenti

The Office Action cited Lucenti ((2004) *The Scientist* 18:1; "Lucenti"), and stated that Lucenti teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong.

The instant application provides a correlation between patient response to treatment with an EGFR inhibitor and expression levels of particular mRNAs. In contrast, Lucenti relates to linkage of a particular disease to a particular mutation. As such, Lucenti does not appear to have any relevance to whether the instant claims are enabled.

Lucenti does not contain any disclosure that would cast doubt on a correlation between patient response to an ErbB1 inhibitor an LAMC2 transcript levels. It is incumbent upon the Patent Office, whenever an "enablement" rejection under 35 U.S.C. §112, first paragraph, is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement; otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.[6]

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[6] *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

If the Examiner has specific knowledge as to why a person skilled in the art would doubt that there is a correlation between patient response to an ErbB1 inhibitor an LAMC2 transcript levels, the Examiner is invited to provide an affidavit to that effect, as provided for under 37 C.F.R. §104(d)(2).

Cheung

The Office Action cited Cheung et al. ((2003) *Nat. Genet.* 33:422; "Cheung"), and stated that Cheung teaches that there is natural variation in gene expression among different individuals. The Office Action stated that the claims require a step of determining a "higher normalized level" and stated that the specification is silent as to how much higher the expression needs to be.

As noted in the Example 1, the relationship between gene expression and patient response was evaluated by logistic regression. Expression levels of certain genes were identified as statistically significant, as described. Specification, paragraph 0095. As explained above, determination of a "normalized level" takes into account variations with respect to absolute levels of a transcript. As such, analysis of a normalized level of a transcript, e.g., LAMC2, provides for a correlation with patient response to an ErbB1 inhibitor.

Giaccone

The Office Action cited Giaccone (but did not provide the complete cite) as teaching six EGFR inhibitors (Iressa, Tarceva, lapatinib, cenertinib [*sic*, canertinib], ZD6474, and AEE788), and as teaching that each of these drugs has a different mechanism by which it acts on the EGFR. The Office Action concluded that "it is unpredictable as to whether the results obtained for colon cancer using whichever EGFR inhibitor the inventor used could be extrapolated to other EGFR inhibitors because each inhibitor works by a different mechanism." Office Action, page 12.

However, the Office Action has presented no reasoning as to why the mechanism of action of a given EGFR inhibitor would affect the observed correlation between patient response to an ErbB1 inhibitor and LAMC2 transcript level.

Indeed, as noted above, Applicants provided evidence that LAMC2 transcript levels correlate to patient response to at least three (Tarceva (erlotinib); Iressa (gefitinib), and AEE788) of the ErbB1 inhibitors noted by the Office Action in connection with Giaccone. In addition, as noted above, patient response to ErbB1 inhibitors of various classes (e.g., quinazolines, pyrrolopyrimidine, and monoclonal antibodies) was shown to correlate with LAMC2 transcript levels. As such, a reference that merely teaches that different EGFR inhibitors act by different mechanisms of action does not lead to a conclusion of lack of enablement of the instant claims.

- **quantity of experimentation necessary**

The Office Action stated that the specification does not teach how much of a difference between the observed normalized expression level and the comparison standard would be necessary to draw the conclusion set

forth in the claims. The Office Action stated that one would have to conduct "extensive experimentation" which may involve "treating patients with different types of EGFR inhibitors and conducting multiple gene expression assays to determine the expression levels of LAMC3 and GPC3." Office Action, page 13.

However, as noted above, Applicants have provided evidence of correlation between patient response to a number of ErbB1 inhibitors of various classes and LAMC2 transcript levels. Thus, there would be no need to conduct "extensive experimentation" involving "treating patients with different types of EGFR inhibitors."

Furthermore, as noted above, Applicants have provided evidence of an inverse correlation between patient response to a number of ErbB1 inhibitors of various classes and LAMC2 transcript levels. Measurement of LAMC2 transcript levels is a matter of routine, given the guidance in the specification and the skill level and knowledge in the art. Determination of normalized levels is also a matter of routine, given the guidance in the specification and the skill level and knowledge in the art. As such, there would be no need to conduct "extensive experimentation" involving "conducting multiple gene expression assays."

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[7]

As has been explained[8]:

> "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

The only experiments, if any, that need be performed to enable the entire scope of the claims would involve determining normalized levels of LAMC2 in a patient sample comprising tumor cells. The instant specification provides ample guidance for how to determine such normalized levels. As such, no undue experimentation would be required.

Conclusion as to the rejections under 35 U.S.C. §112, first paragraph

Applicants submit that the rejection of claims 31, 35-38, 41-47, 51, 52, 56, 57, and 59-61 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C. §112, second paragraph

Claims 31, 35-38, 41-47, 51, 52, 56, 57, and 59-61 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

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[7] See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).

Claims 31, 35-38, 41-47, 51, 52, 56, 57, and 59-61

The Office Action stated that claims 31, 35-38, 41-47, 51, 52, 56, 57, and 59-61 are indefinite because they do not clearly set forth a step of predicting the likelihood that a human colon cancer patient will respond to treatment with an ErbB1 inhibitor.

Without conceding as to the correctness of this rejection, claim 31 is amended to recite the step of "analyzing the normalized level of the LAMC2 transcript so as to predict the likelihood of response of the patient to treatment with an ErbB1 inhibitor based on the normalized level of the LAMC2 transcript."

"higher normalized level"

The Office Action stated: 1) "higher" is a relative term that is not defined by the claims; 2) the specification does not provide a standard for ascertaining the requisite degree; and 3) one of ordinary skill in the art would not be reasonably apprised of the scope. Applicants respectfully traverse the rejection.

The specification describes how the levels of gene expression were measured, normalized, and evaluated. Specification, paragraph 0095. The specification indicates that certain genes were identified as "statistically significant." Those skilled in the art would understand that a "higher" level would refer to a statistically significant higher level.

Nevertheless, and solely in the interest of expediting prosecution, claim 31 is amended to delete the phrase "higher normalized level."

"decreased likelihood"

The Office Action stated: 1) "decreased" is a relative term that is not defined by the claims; 2) the specification does not provide a standard for ascertaining the requisite degree; and 3) one of ordinary skill in the art would not be reasonably apprised of the scope. Applicants respectfully traverse the rejection.

Those skilled in the art would understand that a "decreased likelihood" would refer to a statistically significant decreased likelihood.

Nevertheless, and solely in the interest of expediting prosecution, claim 31 is amended to delete the phrase "decreased likelihood."

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[8] *In re Wands* 8 USPQ 2d at 1404

"elevated"

The Office Action stated that claim 56 is indefinite over the recitation of "expression level of LAMC2 gene is elevated." The Office Action stated: 1) "elevated" is a relative term that is not defined by the claims; 2) the specification does not provide a standard for ascertaining the requisite degree; and 3) one of ordinary skill in the art would not be reasonably apprised of the scope. Applicants respectfully traverse the rejection.

Those skilled in the art would understand that an "elevated level of LAMC2 gene expression" would refer to a level that was elevated to a statistically significant degree over a control.

Claim 57

The Office Action stated that claim 57 is indefinite because the claims do not clearly set forth a step of predicting the likelihood that a human colon cancer patient will respond to treatment with an ErbB1 inhibitor.

Claim 57 is cancelled without prejudice to renewal, thereby rendering this rejection moot.

Conclusion as to the rejections under 35 U.S.C. §112, second paragraph

Applicants submit that the rejection of claims 31, 35-38, 41-47, 51, 52, 56, 57, and 59-61 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§102(b)

Claims 31, 35-37, and 57 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Hlubeck ((2001) *Cancer Res.* 61:8089; "Hlubeck") "as evidenced by Salomon" ((1995) *Crit. Rev. Oncol/Hematol.* 19:183; "Salomon").

The Office Action stated that Hlubek teaches a method comprising determining the expression levels of LAMC2 in cells obtained from patients with colorectal carcinomas; and that Salomon teaches that ~25-77% of colon cancer patients studied have ErbB1 expressing cancer cells. The Office Action stated that Hlubek thus teaches a method of determining expression of the LAMC2 transcript in a sample from a patient with an ErbB1 expressing colon cancer.

Claim 31 is amended to recite "analyzing the normalized level of the LAMC2 transcript so as to predict the likelihood of response of the patient to treatment with an ErbB1 inhibitor based on the normalized level of the LAMC2 transcript." Claim 57 is cancelled without prejudice to renewal, thereby rendering this rejection of claim 57 moot.

Hlubek neither discloses nor suggests a method of predicting the likelihood that a human colon cancer patient will respond to treatment with an ErbB1 inhibitor, the method comprising determining the normalized

level of a LAMC2 transcript and analyzing the normalized level of the LAMC2 transcript so as to predict the likelihood of response of the patient to treatment with an ErbB1 inhibitor based on the normalized level of the LAMC2 transcript, as recited in claim 31. As such, Hlubek cannot anticipate any of claims 31 and 35-37.

Applicants submit that the rejection of claims 31, 35-37, and 57 under 35 U.S.C. §102(b) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejections under 35 U.S.C.§103(a)

Claims 41-47, 52, 59, and 60 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Hlubeck in view of Bao (U.S. Patent No. 6,251,601; "Bao"). Claim 60 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Hlubek in view of Chun ((2000) *J. Korean Med. Sci.* 61:8089. Claim 61 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Hlubek in view of Filmus ((2001) *Glycobiol.* 11:19R; "Filmus").

Claims 41-47, 52, 59, and 60

The Office Action stated that Hlubek does not teach a method wherein the expression of the LAMC2 transcript is determined using a microarray; and stated that Bao teaches that expression can be determined using an array of nucleic acid target elements attached to a solid support. The Office Action concluded that it would have been obvious to modify the method of Hlubek by performing expression analysis on a microarray as suggested by Bao. Applicants respectfully traverse the rejection.

As noted above, claim 31, from which claims 41-47, 52, 59, and 60 directly or indirectly depend, has been amended to recite "analyzing the normalized level of the LAMC2 transcript so as to predict the likelihood of response of the patient to treatment with an ErbB1 inhibitor based on the normalized level of the LAMC2 transcript."

Hlubek neither discloses nor suggests a method of predicting the likelihood that a human colon cancer patient will respond to treatment with an ErbB1 inhibitor, the method comprising determining the normalized level of a LAMC2 transcript and analyzing the normalized level of the LAMC2 transcript so as to predict the likelihood of response of the patient to treatment with an ErbB1 inhibitor based on the normalized level of the LAMC2 transcript, as recited in claim 31.

Bao does not cure the deficiency of Hlubek. Bao is cited merely for discussing expression analysis on a microarray.

Hlubek, alone or in combination with Bao, neither discloses nor suggests the method as recited in claim

31. As such, Hlubek, alone or in combination with Bao, cannot render any of claims 41-47, 52, 59, and 60 obvious.

Claim 60

The Office Action stated that Hlubek does not teach a method wherein the expression of CD44v6 is also determined. Chun was cited as teaching determining the expression level of CD44v6 in colorectal tumors.

As noted above, claim 31, from which claim 60 depends, has been amended to recite "predicting the likelihood of response of the patient to treatment with an ErbB1 inhibitor based on the normalized level of the LAMC2 transcript."

Hlubek neither discloses nor suggests a method of predicting the likelihood that a human colon cancer patient will respond to treatment with an ErbB1 inhibitor, the method comprising determining the normalized level of a LAMC2 transcript and analyzing the normalized level of the LAMC2 transcript so as to predict the likelihood of response of the patient to treatment with an ErbB1 inhibitor based on the normalized level of the LAMC2 transcript, as recited in claim 31.

Chun does not cure the deficiency of Hlubek. Chun is cited merely for discussing determining the expression level of CD44v6 in colorectal tumors.

Hlubek, alone or in combination with Chun, neither discloses nor suggests the method as recited in claim 60. As such, Hlubek, alone or in combination with Chun, cannot render claim 60 obvious.

Claim 61

The Office Action stated that Hlubek does not teach a method wherein both LAMC2 and GPC3 are assayed. Filmus was cited as teaching determining the expression level of GPC3 in colorectal tumors.

Claim 61 is cancelled without prejudice to renewal, thereby rendering this rejection of claim 61 moot.

Conclusion as to the rejections under 35 U.S.C. §103(a)

Applicants submit that the rejection of claims 41-47, 52, 59, and 60, and the rejection of claim 60, under 35 U.S.C. §103(a) have has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejections.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number GHDX-005.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: April 17, 2008

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National Cancer Institute
U.S. National Institutes of Health | www.cancer.gov

Dictionary of Cancer Terms

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EGFR

The protein found on the surface of some cells and to which epidermal growth factor binds, causing the cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, so these cells may divide excessively in the presence of epidermal growth factor. Also called epidermal growth factor receptor, ErbB1, and HER1.

Previous Definitions: efficacy, effusion, eflornithine, EFTs, EGb761
Next Definitions: ejaculation, EKB-569, electroacupuncture, electroconvulsive therapy, electrode

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Dictionary of Cancer Terms

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ErbB1

Epidermal growth factor receptor. The protein found on the surface of some cells and to which epidermal growth factor binds, causing the cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, so these cells may divide excessively in the presence of epidermal growth factor. Also called epidermal growth factor receptor, EGFR, and HER1.

Previous Definitions: ER, ER+, ER-, ERA-923, erb-38 immunotoxin
Next Definitions: Erbitux, ERCP, erectile dysfunction, erection, erlotinib